

**REMARKS****Claim Status**

This paper is responsive to the Office Action mailed August 20, 2008. By the present amendment, Claims 1 and 5 are pending in the Application. With this response, Claim 1 and 5 are amended and Claim 2 is cancelled. Claims 3, 4 and 6 – 20 have been withdrawn as being drawn to previously non-elected subject matter in response to the restriction requirement. Applicants expressly reserve the right to file one or more divisional applications directed to the withdrawn, non-elected subject matter during the pendency of this application.

Claim 1 is amended to recite a synthetic CXCR3 polypeptide ligand having a sequence of SEQ ID NO: 15. Claim 5 is amended to recite a composition having the synthetic CXCR3 ligand of Claim 1. No new matter is added. Accordingly, entry of the amendments and reconsideration of the amendments are respectfully requested.

**The Claim Rejection Under 35 U.S.C § 112, first paragraph for Lack of Enablement should be Withdrawn:**

Claims 1, 2 and 5 are rejected under 35 U.S.C § 112, first paragraph as allegedly failing to comply with the enablement requirement.

Without conceding to the rejections, Claim 1 is amended to recite a synthetic CXCR3 polypeptide ligand having a sequence of SEQ ID NO: 15, thus incorporating the limitation of Claim 2. Claim 5 is amended to recite a composition having the synthetic CXCR3 ligand of Claim 1. Claim 2 have been cancelled, thus obviating the Examiner's rejection.

The test for enablement is whether one reasonably skilled in the art could make or use the invention without undue experimentation from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). Claim 1 as amended specifically discloses the amino acid sequence of the synthetic CXCR3 polypeptide having SEQ ID NO: 15. Because Claim 1 now recites SEQ ID NO: 15, one of ordinary skill in the art reading the information disclosed throughout the specification coupled with what is known in the art at the time the patent application was filed would be able to make and use the invention. (*See, inter alia* at p. 10 - 13, [0109] – [0134] and p 24, [0268] – [0275]).

The Examiner asserts that the specification provides “little or no guidance beyond [ ] sequence data to enable one of ordinary skill in the art to determine, without undue experimentation ...” and “[t]he art recognizes that function cannot be predicted from structure alone.” The Examiner cites Bork; Skolnick and Fetrow; Doerks et al; Smith and Zhang; Brenner; Bork and Bairoch; and Ferrer-Costa in support of the assertion. Applicants respectfully traverse in that the proteins described in these references are distinct from those in the presently claimed invention. The proteins described in these references are unknown proteins for which a function is to be ascribed to them based on known structures and vice versa. On the other hand, like the immunoglobulin chimeric proteins, Applicants’ CXCR3 synthetic polypeptide ligand (herein refer to as synthetic polypeptide) is composed of known subsequences from three very well known chemokines. These chemokines used in the making of the synthetic polypeptide

have highly conserved amino acid sequences with known structures and functions. Thus it does not rely on the structure of the synthetic polypeptide alone to predict its function.

Specifically, Applicants respectfully refer the Examiner to Scolnick and Fetrow at p. 36, rt. col. ll. 1-6, which states that “[f]or proteins whose sequences identity is above ~30%, one can use homology modeling to build the structure.” However, structure prediction is far more difficult for proteins that are not homologous to proteins with known structure.” Applicants’ synthetic polypeptide ligand is constructed from three different but well known chemokines (I-TAC, IP-10 and Mig) that are (1) highly conserved in their sequences (> 30% homology; *See* FIG 2); (2) very similar in their functions (*i.e.* bind to and activate the CXCR3 chemokine receptor to cause  $\text{Ca}^{+2}$  level changes and control leukocyte migration); and (3) known to be structurally and functionally similar. Thus, Applicants’ synthetic polypeptide does not rely on the structure of the synthetic polypeptide alone to predict its function and the references do not apply to Applicant’s invention.

In addition, the Examiner further cites Wells (Biochemistry 29:8509), Ngo et al. (“The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14) to support his view that changes in the protein amino acid sequence, including similar substitutions would affect the folding of the protein and hence its function.

Wells provides that although mutations in proteins may be additive, “[i]n the majority of cases, combination of mutations that affect substrate or transition-state binding and protein-protein interaction”, .... “are unlikely to alter grossly the structure and mode of binding.” (*See*, p. 8515, rt. col, 1<sup>st</sup> paragraph under “CONCLUSIONS”). Because Applicants’ synthetic CXCR3 polypeptide ligand is derived by “joining” in-sequence distinct subsequences of the various

domains of the three chemokine ligands that are highly conserved in their amino acid sequences (See, Fig 2 for alignment of all three sequences) at the specific “break-points” between domains and subdomains with no amino acid changes being made within these domains and subdomains, it is unlikely that such a synthetic polypeptide would not fold into its correct 3-dimensional structure and retain its functional activity. Thus, a person having ordinary skill in the art reading the specification as disclosed and using the techniques and skills routinely used in the field of molecular biology/biochemistry will be able to practice the invention without any undue experimentation and still be able to obtain a synthetic polypeptide that is correctly folded and retain the function of a chemokine.

Ngo teaches the use of mathematical computation to predict the native fold of unknown proteins based on amino acid sequences without taking into account physiological environment. On the other hand, Applicants invention is not based on the use of a mathematical algorithm to predict the folding of unknown proteins. The structure and function of chemokine ligands, I-TAC, IP-10 and Mig are well known in the field of chemokine and Applicants have carefully designed the synthetic polypeptide to enhance or minimize certain functions (e.g. receptor activation, calcium mobilization *etc*) by swapping these domains at specific “break-points” within the domain and subdomains from all these three chemokines.

The Examiner further asserts that the specification does not teach whether or not SEQ ID NO:15 has any activity similar to IP-10, I-TAC or Mig nor any working example for the treatment of diseases with either SEQ ID NO: 15 or any of the other variants.

At the outset, Applicants respectfully point out that a working example need not be disclosed in order to satisfy the enablement requirement of 35 U.S.C § 112, first paragraph (See,

*M.P.E.P.*, 8<sup>th</sup> Edition, Revision 6, Vol. 2, September 2007), § 2164.02 at 2100-196, left col., first paragraph) and further remind the Examiner that it is inappropriate to conclude that experimentation is undue based on the mere unpredictability of the results of an experiment. Furthermore, “[a]n applicant need not have actually reduced the invention to practice prior to filing. *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987).

As discussed above, the structures and functions of the I-TAC, IP-10 and Mig used in constructing the synthetic peptides are highly conserved. For example, all amino acid sequences in all three ligands are highly conserved – the signal sequence is from amino acids 1-21/22 followed by the CXC motif domain, amino acids 22 to 94 (I-TAC), 22 to 98 for IP-10 and 23-125 for Mig. All three chemokines contain the same basic structure - a CXC domain containing subdomains: (1) the triggering domain from amino acids 22-31 (this triggering domain cause activation of the receptor upon binding to the receptor via the docking loop) at the N-terminus of the matured protein after the signal sequence have been cleave off, and (2) the docking loop from amino acids 32-38. The CXC domain containing both the triggering domain and docking loop is then followed by two strands at about amino acids 45 to about amino acid 69 and a helix from about amino acid 80 to about amino acid 89. There are two disulfide bonds between amino acids 30 and 57, and 32 and 74.

Applicants respectfully refer the Examiner to the specification at, *inter alia*, p. 8, [0078] to [0089] and FIGS. 2-8, and p. 10 -13, [0110] – [0134] for making the synthetic polypeptides in the present invention. These constructs specifically described specific amino acid sequences for the various domains that are reflected in the various domains described above paragraph and are joined at the specific ‘break-points’ delineated by each of the domains and subdomains. A

person having ordinary skill in the art reading the specification as disclosed and using the techniques and skills routinely used in the field of molecular biology/biochemistry and chemokine biology will be able to practice the invention without any undue experimentation. Furthermore, since the domains in the synthetic polypeptide are similar to those of the native ligands, the ability to activate and mobilize CXCR3 receptors to result in enhanced or diminished activity will depend on sequences of the triggering and docking domains of the polypeptide replaced.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 112, 1<sup>st</sup> paragraph on enablement be withdrawn.

**The Claim Rejection Under 35 U.S.C § 112, first paragraph for lack of Written Description Should be Withdrawn:**

Claims 1, 2 and 5 are rejected under 35 U.S.C § 112, first paragraph as allegedly failing to comply with the written description requirement.

The test for sufficiency of written description is whether the disclosure of the application “reasonably conveys to the artisan that the inventor had possession of the claimed subject matter.” *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that the applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any

description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognized that the inventor had possession of the claimed invention. (*See, M.P.E.P.*, 8<sup>th</sup> Edition, Revision 6, Vol. 2, September 2007), § 2163 IIA.3(a) at 2100-178, left col., last paragraph)

Applicants respectfully submit that the written description as disclosed in the specification at, *inter alia*, p. 8, [0078] to [0089] coupled with FIGS. 2-8, and p. 10-13, [0110] – [0134] for making the synthetic polypeptides in the present invention, along with the general knowledge known in the field of chemokine, is adequately written for the synthetic polypeptide as claimed and thus is in possession of the claim invention. The specification specifically provides the various amino acid sequences from the different domains of the three chemokines used for making the synthetic polypeptide. These sequences with the various domains are aligned and are shown in FIG. 2. The alignments clearly indicate the locations where the various domain breaks can be used for replacing the various subsequences in the synthetic polypeptides as illustrated in SEQ ID NO: 15. Thus, the synthetic polypeptide as claimed in the present invention is adequately described and Applicants assert that a person skilled in the art would clearly recognize that the Applicants are in possession of the claimed invention.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 112, 1<sup>st</sup> paragraph on written description be withdrawn.

**The Claim Rejection Under 35 U.S.C § 102 Should be Withdrawn:**

(a) Claims 1 and 5 are rejected under (a) 35 U.S.C § 102 (b) as being anticipated by Barone (May 5 – 10, 2002) and (b) 35 U.S.C § 102 (a) as being anticipated by Clark-Lewis *et al.* (November 1, 2002).

As discussed above, the present invention is directed to a synthetic CXCR3 polypeptide ligand having an amino acid sequence that are composed of discrete amino acid subsequences derived from IP-10, ITAC and Mig. (See, claims 1, 2, and 23).

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference.” *Vardegaal Bros. v. Union Oil Co of California*, 814 F.2d 628, 631 (Fed Cir. 1987).

(a) Barone teaches a recombinant lentiviral mediated expression of a full length Mig-IP10 fusion gene in the corneal of a rabbit. Barone does not teach a recombinant or synthetic CXCR3 polypeptide ligand having an amino acid subsequences from each of the CXCR3 ligand, IP-10, ITAC and Mig.

(b) Clark-Lewis *et al.* teach IP-10/ITAC hybrid molecules (I-TAC-H1, I-TAC-H2, and I-TAC-H3, See FIG 4). Clark does not teach or disclose a hybrid molecule having amino acid sequences from I-TAC, IP-10, and Mig.

Furthermore, Applicants have amended independent Claim 1 to include the limitation of dependent Claim 2 having SEQ ID NO: 15. Similarly, Claim 5 is amended to recite the limitation in Claim 1. Because both Claims 1 and 5 now recites SEQ ID NO: 15, a sequence that is not taught in Barone or Clark-Lewis *et al.*, Applicants respectfully request that the rejection under 35 U.S.C. § 102 (b) and (a) be withdrawn.

In summary, none of the references applied by the Examiner under 35 U.S.C. § 102(b) or 102 (a) expressly teach each and every element of Applicants' novel synthetic CXCR3

polypeptide ligand of SEQ ID NO: 15 comprising amino acid sequences from all three chemokine receptor ligands, IP-1-, ITAC and Mig as presented in claims of the present invention. Because none of the references applied by the Examiner expressly or inherently discloses Applicants' synthetic CXCR3 polypeptide ligand, these references cannot be said to anticipate Applicants' novel synthetic CXCR3 polypeptide ligand. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 102 (b) and (a) be withdrawn.

### **CONCLUSION**

In light of the above amendments and remarks, Applicants respectfully submit that claims 1 and 21 satisfy all criteria for patentability and are in condition for allowance. Applicants request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney, if a telephone call could help resolve any remaining issues.

Pursuant to 37 CFR § 1.136(a)(3), the Commissioner is hereby authorized to charge all required fees, including fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Deposit Account No. 50-1283.

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Respectfully submitted,

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